L16 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:139868 HCAPLUS

DOCUMENT NUMBER: 130:196958

TITLE: Preparation of 3-tert-butyl-L-tyrosinamide-containing

peptides and related compounds exhibiting a motilin

receptor antagonism

INVENTOR(S): Kotake, Ken-ichiro; Kozono, Toshiro; Sato,

Tsutomu; Takanashi, Hisanori

PATENT ASSIGNEE(S): Chuqai Seiyaku Kabushiki Kaisha, Japan

SOURCE: PCT Int. Appl., 144 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.					KIND		DATE		APPLICATION NO.					DATE					
WO						A1		19990225		WO 1998-JP3627					19980814				
	W:	AL,	AM,	AT,	ΑU,	ΑZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CU,	CZ,	DE,		
		DK,	EE,	ES,	FΙ,	GB,	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IS,	KΕ,	KG,	KR,		
		KΖ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,		
		PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ΤJ,	TM,	TR,	TT,	UA,	UG,		
		US,	UZ,	VN,	YU,	ZW													
	RW:	GH,	GM,	KΕ,	LS,	MW,	SD,	SZ,	UG,	ZW,	AT,	BE,	CH,	CY,	DE,	DK,	ES,		
		FΙ,	FR,	GB,	GR,	ΙE,	ΙT,	LU,	MC,	NL,	PT,	SE,	BF,	ΒJ,	CF,	CG,	CI,		
		CM,	GΑ,	GN,	GW,	ML,	MR,	ΝE,	SN,	TD,	TG								
TW	460478				В	20011021 TW 19					L998-	998-87113211 19980811					811		
CA					A1					CA 1998-2301687									
AU						A 19990308 AU 1998-86490								19980814					
					B2 20011129														
									JP 1998-229586					19980814					
	3583						2004												
EP								EP 1998-937826											
	R:	•	•	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	MC,	PT,		
		IE,																	
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										WO 1	L998-	JP36	27	٦	W 1	.9980	814		
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OTHER SOURCE(S): MARPAT 130:196958

GΙ

ΙI

AΒ Phenethylamine derivs. represented by general formula [I; wherein A represents an amino acid or  $\alpha$ -substituted amino acid residue; R1 represents R6CO, (un)substituted C2-7 linear or branched alkyl, C3-8 alkenyl, or C3-8 alkynyl; R2 represents hydrogen, C1-3 linear or branched alkyl; R3 represents COR7, (un) substituted C1-5 linear or branched alkyl, C2-5 alkenyl, or C2-5 alkynyl; R4 represents H, C1-6 linear or branched alkyl, C2-6 alkenyl, C2-6 alkynyl, etc.; R5 represents hydroxy or C1-4 n-alkoxy; R6 represents (un)substituted C1-6 linear or branched alkyl, C2-7 alkenyl, or C2-7 alkynyl, optionally benzene- or heterocyclic ring-condensed C3-7 cycloalkyl, (un)substituted C6-12 aromatic ring, (un) substituted C3-12 (un) saturated heterocyclic ring, (un) substituted NH2, (un) substituted linear or branched C1-5 alkoxy, C2-6 alkenyloxy, C2-6 alkynyloxy, etc.; and R7 represents H, (un)substituted C1-5 linear or branched alkyl, C3-7 cycloalkyl, (un)substituted NH2, OH, linear or branched alkyl C1-6 alkoxy, or C3-7 cycloalkyloxy] are prepared Also claimed are a motilin receptor antagonist, an inhibitor of digestive tract motility, and a remedy for high blood motilin. They are also useful for the treatment of irritable bowel syndrome. Thus,  $N\alpha$ -methyl-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-Lvalinamide was condensed with Boc-Phe-OH using HOBT and DIC in DMF at room temperature for 2.5 days followed by deprotection with CF3CO2H in CH2C12 to give

the title compound (II). II in vitro showed IC50 of 1.9 nM for inhibiting the binding of [125I]motilin motilin receptor preparation from rabbit ileum mucous membrane.

IT 220806-45-1P 220806-47-3P 220806-49-5P 220806-51-9P 220806-59-7P 220806-61-1P 220806-63-3P 220806-71-3P 220806-75-7P 220806-77-9P 220806-79-1P 220806-81-5P 220806-83-7P 220806-85-9P 220806-87-1P 220806-89-3P 220806-91-7P 220806-93-9P

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220806-95-1P 220806-97-3P 220806-99-5P
     220807-01-2P 220807-03-4P 220807-05-6P
     220807-07-8P 220807-09-0P 220807-11-4P
     220807-19-2P 220808-16-2P 220808-17-3P
     220808-18-4P 220808-19-5P 220808-20-8P
     220808-27-5P 220808-28-6P
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of 3-tert-butyl-L-tyrosinamide-containing peptide compds. as
        motilin receptor antagonists, inhibitors of digestive tract motility,
        and remedy for high blood motilin)
     220806-45-1 HCAPLUS
RN
CN
     L-Tyrosinamide, L-phenylalanyl-L-phenylalanyl-3-(1,1-dimethylethyl)-,
     mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
     CM
          1
     CRN 220806-44-0
     CMF
         C31 H38 N4 O4
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Absolute stereochemistry.

CM 2

CRN 76-05-1

CMF C2 H F3 O2

RN 220806-47-3 HCAPLUS
CN L-Tyrosinamide, L-phenylalanyl-L-valyl-3-(1,1-dimethylethyl)-,
 mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-46-2 CMF C27 H38 N4 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-49-5 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-alanyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-48-4 CMF C25 H34 N4 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-51-9 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-leucyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-50-8 CMF C28 H40 N4 O4

Absolute stereochemistry.

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-59-7 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-tyrosyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-58-6 CMF C31 H38 N4 O5

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-61-1 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl- $(\alpha S)-\alpha$ -aminobenzenebutanoyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-60-0 CMF C32 H40 N4 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-63-3 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-3-(2-thienyl)-L-alanyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-62-2 CMF C29 H36 N4 O4 S

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$${\tiny \begin{array}{c}F\\F-C-CO_2H\\|\\F\end{array}}$$

RN 220806-71-3 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-isoleucyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-70-2 CMF C28 H40 N4 O4

Absolute stereochemistry.

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-75-7 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-3-cyclohexyl-L-alanyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-74-6 CMF C31 H44 N4 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-77-9 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-3-methyl-L-valyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-76-8 CMF C28 H40 N4 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-79-1 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L- $\alpha$ -aspartyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM :

CRN 220806-78-0 CMF C26 H34 N4 O6

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-81-5 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L- $\alpha$ -glutamyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-80-4 CMF C27 H36 N4 O6

Absolute stereochemistry.

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-83-7 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-5-carboxy-L-norvalyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-82-6 CMF C28 H38 N4 O6

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-85-9 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-asparaginyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CRN 220806-84-8 CMF C26 H35 N5 O5

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-87-1 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-glutaminyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-86-0 CMF C27 H37 N5 O5

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-89-3 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-6-oxo-L-lysyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-88-2 CMF C28 H39 N5 O5

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-91-7 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-(2S)-2,4-diaminobutanoyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-90-6 CMF C26 H37 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-93-9 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-ornithyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM :

CRN 220806-92-8 CMF C27 H39 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-95-1 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-lysyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-94-0 CMF C28 H41 N5 O4

Absolute stereochemistry.

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-97-3 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-seryl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220806-96-2 CMF C25 H34 N4 O5

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220806-99-5 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-homoseryl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CRN 220806-98-4 CMF C26 H36 N4 O5

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220807-01-2 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-threonyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220807-00-1

CMF C26 H36 N4 O5

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220807-03-4 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-(2S)-2-aminobutanoyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220807-02-3 CMF C26 H36 N4 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220807-05-6 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-norvalyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220807-04-5 CMF C27 H38 N4 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220807-07-8 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-methionyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220807-06-7 CMF C27 H38 N4 O4 S

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220807-09-0 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-histidyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220807-08-9 CMF C28 H36 N6 O4

Absolute stereochemistry.

CRN 76-05-1 CMF C2 H F3 O2

RN 220807-11-4 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-tryptophyl-3-(1,1-dimethylethyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 220807-10-3 CMF C33 H39 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 220807-19-2 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-N-methyl-L-valyl-3-(1,1-dimethylethyl)(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-16-2 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-L-valyl-3-(1,1-dimethylethyl)-N $\alpha$ -methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-17-3 HCAPLUS

CN L-Valinamide, L-phenylalanyl-N-[(1R)-2-[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-methylethyl]-N2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-18-4 HCAPLUS

CN L-Tyrosinamide, L-phenylalanyl-N-methyl-L-valyl-3-(1,1-dimethylethyl)- N $\alpha$ -methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-19-5 HCAPLUS

CN L-Valinamide, N-methyl-L-phenylalanyl-N-[(1R)-2-[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-methylethyl]-N2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-20-8 HCAPLUS

CN L-Valinamide, L-phenylalanyl-N-[(1R)-2-[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-methylethyl]-N, N2-dimethyl- (9CI) (CA INDEX NAME)

RN 220808-27-5 HCAPLUS

CN L-Tyrosinamide, N-[(2S)-2-amino-3-phenylpropyl]-L-valyl-3-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-28-6 HCAPLUS

CN Butanamide, N-[(1S)-2-amino-1-[[3-(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-2-[[(2S)-2-amino-3-phenylpropyl]amino]-3-methyl-, (2S)- (CA INDEX NAME)

Absolute stereochemistry.

IT 220808-36-6P 220808-44-6P 220808-74-2P

220808-80-0P 220808-85-5P 220808-89-9P

220808-90-2P 220808-96-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 3-tert-butyl-L-tyrosinamide-containing peptide compds. as motilin receptor antagonists, inhibitors of digestive tract motility, and remedy for high blood motilin)

RN 220808-36-6 HCAPLUS

CN L-Tyrosinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-methyl-L-valyl-3-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

RN 220808-44-6 HCAPLUS

CN L-Tyrosinamide, N-[(phenylmethoxy)carbonyl]-L-phenylalanyl-L-valyl-3-(1,1-dimethylethyl)-N $\alpha$ -methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-74-2 HCAPLUS

CN L-Tyrosinamide, N-[(2S)-3-phenyl-2-[[(phenylmethoxy)carbonyl]amino]propyl]-L-valyl-3-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-80-0 HCAPLUS

CN 2,5,8,11-Tetraazadodecanedioic acid, 9-[[3-(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-6-(1-methylethyl)-7-oxo-3-(phenylmethyl)-, 1,12-bis(phenylmethyl) ester, (3S,6S,9S)- (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-85-5 HCAPLUS

CN L-Valinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[(1R)-2-[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-methylethyl]-N2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-89-9 HCAPLUS

CN L-Tyrosinamide, N-[(phenylmethoxy)carbonyl]-L-phenylalanyl-N-methyl-L-valyl-3-(1,1-dimethylethyl)-N $\alpha$ -methyl- (9CI) (CA INDEX NAME)

RN 220808-90-2 HCAPLUS

CN L-Valinamide, N-(1,1-dimethylethyl)-L-phenylalanyl-N-[(1R)-2-[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-methylethyl]-N2-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220808-96-8 HCAPLUS

CN L-Valinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[(1R)-2-[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-methylethyl]-N,N2-dimethyl- (9CI) (CA INDEX NAME)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT